```
     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 08:49:56 ON 11 JAN 2005
L1         18655 S "ADAM"
L2         23400 S DISINTEGRIN OR METALLOPROTEASE?
L3          2132 S L1 AND L2
L4       6866200 S CLON? OR EXPRESS? OR RECOMBINANT
L5          1478 S L3 AND L4
L6         94583 S PROTEOGLYCAN
L7            42 S L5 AND L6
L8            20 DUP REM L7 (22 DUPLICATES REMOVED)
                 E YOSHIMURA K/AU
L9          3773 S E3
                 E NISHIMURA A/AU
L10         1725 S E3
                 E HIKICHI Y/AU
L11          286 S E3
L12         5774 S L9 OR L10 OR L11
L13            0 S L5 AND L12
L14            0 S L1 AND L12

=>
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                   STN Express with Discover!
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 NEWS  7  DEC 09   12 databases to be removed from STN on December 31, 2004
 NEWS  8  DEC 15   MEDLINE update schedule for December 2004
 NEWS  9  DEC 17   ELCOM reloaded; updating to resume; current-awareness
                   alerts (SDIs) affected
 NEWS  10 DEC 17   COMPUAB reloaded; updating to resume; current-awareness
                   alerts (SDIs) affected
 NEWS  11 DEC 17   SOLIDSTATE reloaded; updating to resume; current-awareness
                   alerts (SDIs) affected
 NEWS  12 DEC 17   CERAB reloaded; updating to resume; current-awareness
                   alerts (SDIs) affected
 NEWS  13 DEC 17   THREE NEW FIELDS ADDED TO IFIPAT/IFIUDB/IFICDB
 NEWS  14 DEC 30   EPFULL: New patent full text database to be available on STN
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 NEWS  16 JAN 03   No connect-hour charges in EPFULL during January and
                   February 2005

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               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 10 JANUARY 2005
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                                                   ENTRY    SESSION
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                                                   ENTRY    SESSION
FULL ESTIMATED COST                                 0.21       0.48

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FILE 'LIFESCI' ENTERED AT 08:49:56 ON 11 JAN 2005
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=> s "ADAM"
L1        18655 "ADAM"

=> s disintegrin or metalloprotease?
L2        23400 DISINTEGRIN OR METALLOPROTEASE?

=> s l1 and l2
L3         2132 L1 AND L2

=> s clon? or express? or recombinant
   4 FILES SEARCHED...
L4      6866200 CLON? OR EXPRESS? OR RECOMBINANT

=> s l3 and l4
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L5        1478 L3 AND L4

=> s proteoglycan
L6       94583 PROTEOGLYCAN

=> s l5 and l6
L7          42 L5 AND L6

=> dup rem l7
PROCESSING COMPLETED FOR L7
L8          20 DUP REM L7 (22 DUPLICATES REMOVED)

=> d 1-20 ibib ab

L8   ANSWER 1 OF 20  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2004:546527  HCAPLUS
DOCUMENT NUMBER:          141:99721
TITLE:                    Method of modulating interaction between cell-surface
                          receptor and ligand, particularly, between a
                          fibroblast growth factor receptor and a neural cell
                          adhesion molecule, epitope sequences, and drug
                          screening uses
INVENTOR(S):              Berezin, Vladimir; Albrechtsen, Morten; Bock,
                          Elisabeth
PATENT ASSIGNEE(S):       Enkam Pharmaceuticals A/S, Den.
SOURCE:                   PCT Int. Appl., 154 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
     ---------------      ----   --------    --------------------    --------
     WO 2004056865         A2    20040708    WO 2003-DK901           20031218
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO,
             NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ,
             TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,
             BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE,
             ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK,
             TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.:                       DK 2002-1982        A  20021220
                                             DK 2003-330         A  20030303
AB   The present invention relates to a method for modulating the interaction
     between at least two proteins, wherein at least one of the two proteins is
     a functional cell-surface receptor and the other protein is the receptor
     ligand.  The invention features a binding site of said functional
     cell-surface receptor on the receptor ligand and discloses a series of
     amino acid sequences, which are part of the structure of said binding site
     and/or involved in the interaction between the receptor and the ligand.
     Moreover, the present invention features methods for mol. design and
     screening of a candidate pharmaceutical compound capable of modulating the
     interaction between the functional cell-surface receptor and receptor
     ligand through the described binding site, and provides a screening assay
     for identification of such a compound  The invention further describes an
     antibody capable of binding to the above binding site and/or to an epitope
     comprising an amino acid sequence essential for executing the receptor
     ligand interaction through said binding site.  The invention also concerns
     a variety of uses of the disclosed methods, peptide sequences and
     antibodies.  The invention in preferred embodiments concerns the binding
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site of the fibroblast growth factor receptor (FGFR) on FGFR ligands, compds. capable of modulating the receptor ligand interaction through said binding site, and antibody capable of recognition of said binding site. Drug screening methods for the manufacture of medicaments for the treatment of nervous system diseases and other disorders are claimed.

L8 ANSWER 2 OF 20 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation. on STN

ACCESSION NUMBER: 2004:355817 SCISEARCH
THE GENUINE ARTICLE: 810JX
TITLE: Dysregulated **expression** of adamalysin-thrombospondin genes in human breast carcinoma
AUTHOR: Porter S; Scott S D; Sassoon E M; Williams M R; Jones J L; Girling A C; Ball R Y; Edwards D R (Reprint)
CORPORATE SOURCE: Univ E Anglia, Sch Biol Sci, Norwich NR4 7TJ, Norfolk, England (Reprint); Leicester Royal Infirm, Dept Pathol, Leicester LE2 7LX, Leics, England; Norwich Univ Hosp NHS Trust, Norwich, Norfolk, England; Dept Gen Surg, Norfolk, England; Dept Plast Surg, Norfolk, England; Dept Histopathol, Norfolk, England
COUNTRY OF AUTHOR: England
SOURCE: CLINICAL CANCER RESEARCH, (1 APR 2004) Vol. 10, No. 7, pp. 2429-2440.
Publisher: AMER ASSOC CANCER RESEARCH, 615 CHESTNUT ST, 17TH FLOOR, PHILADELPHIA, PA 19106-4404 USA.
ISSN: 1078-0432.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 49

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The adamalysin-thrombospondin (ADAMTS) proteinases are a relatively newly described branch of the metzincin family that contain metalloproteinase, **disintegrin**, and thrombospondin motifs. They have been implicated in various cellular events, including cleavage of **proteoglycans**, extracellular matrix degradation, inhibition of angiogenesis, gonadal development, and organogenesis. However, in many cases, their normal physiological roles and their potential for dysregulation in malignancy remain to be established. The **expression** profile of ADAMTS1-20 in human breast carcinoma was undertaken by real-time PCR using RNA isolated from malignant tumors, nonneoplastic mammary tissue, and breast cancer cell lines to identify altered regulation that may have potential pathogenetic and prognostic significance. Our studies show that seven of the ADAMTS genes (ADAMTS1, 3, 5, 8, 9, 10, and 18) are consistently down-regulated in breast carcinomas with respect to nonneoplastic mammary tissue, irrespective of the heterogeneity of the samples and the tumor type or grade (Mann-Whitney U test, $P < 0.0001$ for each gene). Conversely, ADAMTS4, 6, 14, and 20 are consistently up-regulated in breast carcinomas ($P = 0.005$, $P < 0.0001$, $P = 0.003$, and $P = 0.001$, respectively). ADAMTS2, 7, 12, 13, 15, 16, 17, and 19 show no significant difference between the sample types. ADAMTS1, 2, 7, 8, 10, and 12 are **expressed** predominantly in stromal fibroblasts. ADAMTS3, 4, 5, 6, 9, and 13-20 inclusive are **expressed** predominantly in myoepithelial cells; all appear to be relatively poorly **expressed** in luminal epithelial cells. ADAMTS15 has emerged as being an independent predictor of survival, with RNA **expression** levels significantly lower ($P = 0.007$) in grade 3 breast carcinoma compared with grade 1 and 2 breast carcinoma.

L8 ANSWER 3 OF 20 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation. on STN

ACCESSION NUMBER: 2003:257823 SCISEARCH
THE GENUINE ARTICLE: 654YF
TITLE: ADAM12/syndecan-4 signaling promotes beta(1) integrin-dependent cell spreading through protein kinase C

alpha and RhoA
AUTHOR: Thodeti C K; Albrechtsen R; Grauslund M; Asmar M; Larsson C; Takada Y; Mercurio A M; Couchman J R; Wewer U M (Reprint)
CORPORATE SOURCE: Univ Copenhagen, Inst Mol Pathol, Frederik Vs Vej 11, DK-2100 Copenhagen, Denmark (Reprint); Univ Copenhagen, Inst Mol Pathol, DK-2100 Copenhagen, Denmark; Lund Univ, Div Mol Med, SE-20502 Malmo, Sweden; Scripps Res Inst, Dept Vasc Biol VB 1, La Jolla, CA 92037 USA; Harvard Univ, Sch Med, Beth Israel Deaconess Med Ctr, Dept Pathol, Boston, MA 02215 USA; Univ London Imperial Coll Sci Technol & Med, Div Biomed Sci, London SW7 2AZ, England
COUNTRY OF AUTHOR: Denmark; Sweden; USA; England
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (14 MAR 2003) Vol. 278, No. 11, pp. 9576-9584.
Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3996 USA.
ISSN: 0021-9258.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 66
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The **ADAMs** (a **disintegrin** and **metalloprotease**) comprise a large family of multidomain proteins with cell-binding and **metalloprotease** activities. The ADAM12 cysteine-rich domain (rADAM12-cys) supports cell attachment using syndecan-4 as a primary cell surface receptor that subsequently triggers beta(1) integrin-dependent cell spreading, stress fiber assembly, and focal adhesion formation. This process contrasts with cell adhesion on fibronectin, which is integrin-initiated but syndecan-4-dependent. In the present study, we investigated ADAM12/syndecan-4 signaling leading to cell spreading and stress fiber formation. We demonstrate that syndecan-4, when present in significant amounts, promotes beta(1) integrin-dependent cell spreading and stress fiber formation in response to rADAM12-cys. A mutant form of syndecan-4 deficient in protein kinase C (PKC)alpha activation or a different member of the syndecan family, syndecan-2, was unable to promote cell spreading. GF109203X and Go6976, inhibitors of PKC, completely inhibited ADAM12/syndecan-4-induced cell spreading. **Expression** of syndecan-4, but not syn4DeltaI, resulted in the accumulation of activated beta(1) integrins at the cell periphery in Chinese hamster ovary beta1 cells as revealed by 12G10 staining. Further, **expression** of myristoylated, constitutively active PKCalpha resulted in beta(1) integrin-dependent cell spreading, but additional activation of RhoA was required to induce stress fiber formation. In summary, these data provide novel insights into syndecan-4 signaling. Syndecan-4 can promote cell spreading in a beta(1) integrin-dependent fashion through PKCalpha and RhoA, and PKCalpha and RhoA likely function in separate pathways.

L8 ANSWER 4 OF 20 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2003223976 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12746310
TITLE: Thyroid hormone enhances aggrecanase-2/**ADAM**-TS5 **expression** and **proteoglycan** degradation in growth plate cartilage.
AUTHOR: Makihira Seicho; Yan Weiqun; Murakami Hiroshi; Furukawa Masae; Kawai Toshihisa; Nikawa Hiroki; Yoshida Eri; Hamada Taizo; Okada Yasunori; Kato Yukio
CORPORATE SOURCE: Department of Prosthetic Dentistry, Hiroshima University Faculty of Dentistry, Minami-ku, Hiroshima 734-8553, Japan.. smakihara@forsyth.org
CONTRACT NUMBER: DE-1455 (NIDCR)
SOURCE: Endocrinology, (2003 Jun) 144 (6) 2480-8.
Journal code: 0375040. ISSN: 0013-7227.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200306
ENTRY DATE: Entered STN: 20030515
Last Updated on STN: 20030626
Entered Medline: 20030625

AB Effects of thyroid hormone on **proteoglycan** degradation in various regions of cartilage were investigated. In propylthiouracil-treated rats with hypothyroidism, **proteoglycan** degradation in epiphyseal cartilage during endochondral ossification was markedly suppressed. However, injections of T(4) reversed this effect of propylthiouracil on **proteoglycan** degradation. In pig growth plate explants, T(3) also induced breakdown of **proteoglycan**. T(3) increased the release of aggrecan monomer and core protein from the explants into the medium. Accordingly, the level of aggrecan monomer remaining in the tissue decreased after T(3) treatment, and the monomer lost hyaluronic acid-binding capacity, suggesting that the cleavage site is in the interglobular domain. The aggrecan fragment released from the T(3)-exposed explants underwent cleavage at Glu(373)-Ala(374), the major aggrecanase-cleavage site. The stimulation of **proteoglycan** degradation by T(3) was less prominent in resting cartilage explants than in growth plate explants and was barely detectable in articular cartilage explants. Using rabbit growth plate chondrocyte cultures, we explored proteases that may be involved in T(3)-induced aggrecan degradation and found that T(3) enhanced the **expression** of aggrecanase-2/**ADAM**-TS5 (a **disintegrin** and a metalloproteinase domain with thrombospondin type I domains) mRNA, whereas we could not detect any enhancement of stromelysin, gelatinase, or collagenase activities or any aggrecanase-1/**ADAM**-TS4 mRNA **expression**. We also found that the aggrecanse-2 mRNA level, but not aggrecanase-1, increased at the hypertrophic stage during endochondral ossification. These findings suggest that aggrecanse-2/**ADAM**-TS5 is involved in aggrecan breakdown during endochondral ossification, and that thyroid hormone stimulates the aggrecan breakdown partly via the enhancement of aggrecanase-2/**ADAM**-TS5.

L8 ANSWER 5 OF 20 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation. on STN
ACCESSION NUMBER: 2003:946369 SCISEARCH
THE GENUINE ARTICLE: BX66F
TITLE: Use of anti-neoepitope antibodies for the analysis of degradative events in cartilage and the molecular basis for neoepitope specificity
AUTHOR: Mort J S (Reprint); Flannery C R; Makkerh J; Krupa J C; Lee E R
CORPORATE SOURCE: Shriners Hosp Children, Joint Dis Lab, 1529 Cedar Ave, Montreal, PQ H3G 1A6, Canada (Reprint); Shriners Hosp Children, Joint Dis Lab, Montreal, PQ H3G 1A6, Canada; McGill Univ, Dept Surg, Montreal, PQ H3A 2T5, Canada; Univ Cardiff, Connect Tissue Biol Lab, Cardiff Sch Biosci, Cardiff, S Glam, Wales
COUNTRY OF AUTHOR: Canada; Wales
SOURCE: PROTEASES AND THE REGULATION OF BIOLOGICAL PROCESSES, (NOV 2003) Vol. 70, pp. 107-114.
Publisher: PORTLAND PRESS LTD, 59 PORTLAND PL, LONDON W1N 3AJ, ENGLAND.
ISSN: 0067-8694.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 18
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Degradation of the cartilage **proteoglycan**, aggrecan, is an

essential aspect of normal growth and development, and of joint pathology. The roles of different proteolytic enzymes in this process can be determined from the sites of cleavage in the aggrecan core protein, which generates novel termini (neoepitopes). Antibodies specific for the different neoepitopes generated by such cleavage events provide powerful tools with which to analyse these processes. The same approach can be used to differentiate the processed, active forms of proteases from their inactive pro-forms. Since the proteolytic processing of these enzymes requires the removal of the inhibitory pro-region, it also results in the generation of N-terminal neoepitopes. Using the newborn rat long bone as a model system, it was shown that the active form of ADAMTS-4 [**ADAM** (a **disintegrin** and metalloproteinase) with thrombospondin motifs-4], but not ADAMTS-5, co-localizes with the aggrecan cleavage neoepitopes known to be produced by this metalloproteinase. Thus, in long bone growth, aggrecan turnover seems to be dependent on ADAMTS-4 activity. To demonstrate the molecular basis of the specificity of anti-neoepitope antibodies, the Fv region of a monoclonal antibody specific for a neoepitope generated by the ADAMTS-4-mediated cleavage of aggrecan has been modelled and the binding of the peptide epitope simulated. In the docked structure, the N-terminus of the peptide antigen is clearly buried in the binding-site cavity. The absence of an open cleft makes it impossible for the intact substrate to pass through the binding site, providing a rationale for the specificity of this class of antibodies.

L8 ANSWER 6 OF 20 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:937303 HCAPLUS
DOCUMENT NUMBER: 138:20443
TITLE: Endocrine disruptor screening using DNA chips of endocrine disruptor-responsive genes
INVENTOR(S): Kondo, Akihiro; Takeda, Takeshi; Mizutani, Shigetoshi; Tsujimoto, Yoshimasa; Takashima, Ryokichi; Enoki, Yuki; Kato, Ikunoshin
PATENT ASSIGNEE(S): Takara Bio Inc., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 386 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
JP 2002355079	A2	20021210	JP 2002-69354		20020313
PRIORITY APPLN. INFO.:			JP 2001-73183	A	20010314
			JP 2001-74993	A	20010315
			JP 2001-102519	A	20010330

AB A method and kit for detecting endocrine-disrupting chems. using DNA microarrays are claimed. The method comprises preparing a nucleic acid sample containing mRNAs or cDNAs originating in cells, tissues, or organisms which have been brought into contact with a sample containing the endocrine disruptor. The nucleic acid sample is hybridized with DNA microarrays having genes affected by the endocrine disruptor or DNA fragments originating in these genes have been fixed. The results obtained are then compared with the results obtained with the control sample to select the gene affected by the endocrine disruptor. Genes whose **expression** is altered by tri-Bu tin, 4-octaphenol, 4-nonylphenol, di-N-Bu phthalate, dichlorohexyl phthalate, octachlorostyrene, benzophenone, diethylhexyl phthalate, diethylstilbestrol (DES), and 17-β estradiol (E2), were found in mice by DNA chip anal.

L8 ANSWER 7 OF 20 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation. on STN
ACCESSION NUMBER: 2001:710786 SCISEARCH
THE GENUINE ARTICLE: 467RY

TITLE: **ADAM**-10 protein is present in human articular cartilage primarily in the membrane-bound form and is upregulated in osteoarthritis and in response to 1L-1 alpha in bovine nasal cartilage

AUTHOR: Chubinskaya S (Reprint); Mikhail R; Deutsch A; Tindal M H

CORPORATE SOURCE: Rush Med Coll, Rush Presbyterian St Lukes Med Ctr, Dept Biochem, 1653 W Congress Pkwy, Chicago, IL 60612 USA (Reprint); Rush Med Coll, Rush Presbyterian St Lukes Med Ctr, Dept Biochem, Chicago, IL 60612 USA; Rush Med Coll, Rush Presbyterian St Lukes Med Ctr, Rheumatol Sect, Chicago, IL 60612 USA; Procter & Gamble Pharmaceut Inc, Hlth Care Res Ctr, Mason, OH USA

COUNTRY OF AUTHOR: USA

SOURCE: JOURNAL OF HISTOCHEMISTRY & CYTOCHEMISTRY, (SEP 2001) Vol. 49, No. 9, pp. 1165-1176.
Publisher: HISTOCHEMICAL SOC INC, UNIV WASHINGTON, DEPT BIOSTRUCTURE, BOX 357420, SEATTLE, WA 98195 USA.
ISSN: 0022-1554.

DOCUMENT TYPE: Article; Journal

LANGUAGE: English

REFERENCE COUNT: 32

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The objective of our study was to determine the tissue distribution and localization of **ADAM**-10 protein in human and bovine cartilage and the changes it undergoes with cartilage degeneration seen in osteoarthritis (OA) and under the influence of interleukin-1 (IL-1). Human normal and OA articular cartilage and bovine nasal cartilage cultured in the presence of IL-1 alpha were processed for histology and immunohistochemistry. **ADAM**-10 protein was extracted from human cartilage and analyzed by Western blotting using anti-**ADAM**-10 antibodies. Fluor 5 Image analyzer and Quantity One software program were applied to quantify the total amount of **ADAM**-10. **ADAM** -10 protein was detected in both human and bovine cartilage. The strongest immunostaining was found in the cytoplasm and/or cell membranes of the superficial and upper middle layer of normal adult human cartilage, in the clusters and fibrillated areas of OA cartilage, and in IL-1 alpha -stimulated bovine nasal cartilage. The distribution of **ADAM**-10 protein in bovine nasal cartilage was dependent on the length of exposure to IL-1 alpha and corresponded to the areas of **proteoglycan** depletion. By Western blotting analysis of human cartilage, **ADAM** -10 was primarily detected in the membrane-enriched fraction and its levels were increased in degenerated and OA cartilage compared to normal cartilage. The results of this study suggest that **ADAM**-10 might be an important factor associated with cartilage degenerative processes.

L8 ANSWER 8 OF 20 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN

ACCESSION NUMBER: 2001:313587 BIOSIS

DOCUMENT NUMBER: PREV200100313587

TITLE: RPE cells **express** several members of the metallo-**disintegrin** (**ADAM**) family of extracellular matrix modifying enzymes.

AUTHOR(S): Mckie, J. N. [Reprint author]; Bevitt, D. J. [Reprint author]; Lorite, M. J. [Reprint author]; Pimenides, D. [Reprint author]; Clarke, M. P.; Langton, K. P.; Barker, M. D.

CORPORATE SOURCE: Medical School, University of Newcastle, Newcastle Upon Tyne, UK

SOURCE: IOVS, (March 15, 2001) Vol. 42, No. 4, pp. S222. print.
Meeting Info.: Annual Meeting of the Association for Research in Vision and Ophthalmology. Fort Lauderdale, Florida, USA. April 29-May 04, 2001.

DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)

LANGUAGE: English
ENTRY DATE: Entered STN: 4 Jul 2001
Last Updated on STN: 19 Feb 2002

L8 ANSWER 9 OF 20 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation. on STN
ACCESSION NUMBER: 2001:365908 SCISEARCH
THE GENUINE ARTICLE: 425LD
TITLE: A **disintegrin** and **metalloprotease** with thrombospondin type1 motifs (ADAMTS-1) and IL-1 receptor type 1 mRNAs are simultaneously induced in nerve injured motor neurons
AUTHOR: Sasaki M; Seo-Kiryu S; Kato R; Kita S; Kiyama H (Reprint)
CORPORATE SOURCE: Osaka City Univ, Grad Sch Med, Dept Anat, Abeno Ku, 1-4-3 Asahimachi, Osaka 5458585, Japan (Reprint); Osaka City Univ, Grad Sch Med, Dept Anat, Abeno Ku, Osaka 5458585, Japan; Asahikawa Med Coll, Dept Oral & Maxillofacial Surg, Asahikawa, Hokkaido 0788510, Japan; Asahikawa Med Coll, Dept Anat, Asahikawa, Hokkaido 0788510, Japan
COUNTRY OF AUTHOR: Japan
SOURCE: MOLECULAR BRAIN RESEARCH, (18 APR 2001) Vol. 89, No. 1-2, pp. 158-163.
Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS.
ISSN: 0169-328X.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 24
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Following rat hypoglossal nerve injury, **expression** of mRNAs for a **disintegrin** and **metalloprotease** with thrombospondin type 1 motifs (ADAMTS-1) and IL-I receptor type 1 (n-1RT1) are induced in the injured motor neurons. Although N1E-115 (N1E) cells, which were treated with IL-1 alpha. showed no alteration of ADAMTS-1 mRNA **expression**, a substantial increase of ADAMTS-1 mRNA **expression** was observed in the N1E cells **expressing** IL-1RT1. These findings suggest that nerve injury promotes IL-1RT1 **expression** in the injured neurons and thereby ADAMTS-1 transcription was induced in response to IL-1 released from glial cells.

L8 ANSWER 10 OF 20 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:175926 HCAPLUS
DOCUMENT NUMBER: 132:218866
TITLE: **Cloning** of cDNA for novel human **ADAM** family protein and its clinical use
INVENTOR(S): Yoshimura, Koji; Hikichi, Yuichi; Nishimura, Atsushi
PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
SOURCE: PCT Int. Appl., 109 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000014227	A1	20000316	WO 1999-JP4766	19990902
W: AE, AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK,				

ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2341327	AA	20000316	CA 1999-2341327		19990902
AU 9954479	A1	20000327	AU 1999-54479		19990902
JP 2000139480	A2	20000523	JP 1999-248436		19990902
EP 1111047	A2	20010627	EP 1999-940629		19990902
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
US 6680189	B1	20040120	US 2001-786256		20010510
US 2004132157	A1	20040708	US 2003-726148		20031202
PRIORITY APPLN. INFO.:			JP 1998-250115	A	19980903
			WO 1999-JP4766	W	19990902
			US 2001-786256	A3	20010510

AB The cDNA encoding a novel protein belonging to the **ADAM** (a **disintegrin** and **metalloprotease**) family are isolated from human and its amino acid sequence deduced. The amino acid sequences deduced from **clone** pTB2052 and **clone** pTB2053 are comprised of 775 and 540 residues, resp. Methods of screening the agonists or the antagonists of protease or extracellular matrix-degrading enzyme by using the protein; prophylactics or therapeutics containing the protein for disk hernia, sciatic neuralgia, glomerulonephritis nephritis, diabetic nephropathy, hepatic fibrosis, lung fibrosis, osteopetrosis; methods of screening **proteoglycan**-degrading enzymes and their agonists or antagonists; and transgenic animals **expressing** the gene are claimed.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 11 OF 20 MEDLINE on STN

ACCESSION NUMBER: 2000270266 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10809781
TITLE: Role of Src kinases in the **ADAM**-mediated release of L1 adhesion molecule from human tumor cells.
AUTHOR: Gutwein P; Oleszewski M; Mechtersheimer S; Agmon-Levin N; Krauss K; Altevogt P
CORPORATE SOURCE: Tumor Immunology Programme, 0710, German Cancer Research Center, D-69120 Heidelberg, Germany.
SOURCE: Journal of biological chemistry, (2000 May 19) 275 (20) 15490-7.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000629
Last Updated on STN: 20000629
Entered Medline: 20000621

AB The ectodomain of certain transmembrane molecules can be released by proteolysis, and the solubilized antigens often exert important biological functions. We demonstrated before that the L1 adhesion molecule is shed from the cell surface. Here we show that L1 release in AR breast carcinoma cells is mediated by a member of the **disintegrin** metalloproteinase (**ADAM**) family of proteinases. Up-regulation of L1 shedding by phorbol ester or pervanadate involved distinct mechanisms. Pervanadate induced shedding and rounding-up of cells from the substrate, which was blocked by the Src kinase inhibitor PP2. Tyr phosphorylation of the L1 cytoplasmic tail and the Src kinase Fyn was observed following pervanadate treatment. Up-regulation of L1 release and activation of Fyn occurred also when cells were detached by EDTA suggesting that the regulation of L1 shedding by this pathway was linked to cell morphology and adhesion. The phorbol 12-myristate 13-acetate-induced shedding was inhibited by the protein kinase C inhibitor bisindolylmaleimide I and by PD98059, a specific inhibitor of

the mitogen-activated protein kinase pathway. Soluble L1 binds to the **proteoglycan** neurocan and in bound form could support integrin-mediated cell adhesion and migration. We propose that the release of cell-associated adhesion molecules such as L1 may be relevant to promote cell migration.

L8 ANSWER 12 OF 20 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2000293210 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10831617
TITLE: The cysteine-rich domain of human **ADAM** 12 supports cell adhesion through syndecans and triggers signaling events that lead to beta1 integrin-dependent cell spreading.
COMMENT: Comment in: J Cell Biol. 2000 May 29;149(5):995-8. PubMed ID: 10831602
AUTHOR: Iba K; Albrechtsen R; Gilpin B; Frohlich C; Loechel F; Zolkiewska A; Ishiguro K; Kojima T; Liu W; Langford J K; Sanderson R D; Brakebusch C; Fassler R; Wewer U M
CORPORATE SOURCE: The Institute of Molecular Pathology, University of Copenhagen, 2100 Copenhagen, Denmark.
CONTRACT NUMBER: CA68494 (NCI)
SOURCE: Journal of cell biology, (2000 May 29) 149 (5) 1143-56. Journal code: 0375356. ISSN: 0021-9525.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200007
ENTRY DATE: Entered STN: 20000714
Last Updated on STN: 20021227
Entered Medline: 20000706

AB The **ADAMs** (a **disintegrin** and **metalloprotease**) family of proteins is involved in a variety of cellular interactions, including cell adhesion and ecto- domain shedding. Here we show that **ADAM** 12 binds to cell surface syndecans. Three forms of **recombinant ADAM** 12 were used in these experiments: the cys-teine-rich domain made in Escherichia coli (rADAM 12-cys), the **disintegrin**-like and cysteine-rich domain made in insect cells (rADAM 12-DC), and full-length human **ADAM** 12-S tagged with green fluorescent protein made in mammalian cells (rADAM 12-GFP). Mesenchymal cells specifically and in a dose-dependent manner attach to **ADAM** 12 via members of the syndecan family. After binding to syndecans, mesenchymal cells spread and form focal adhesions and actin stress fibers. Integrin beta1 was responsible for cell spreading because function-blocking monoclonal antibodies completely inhibited cell spreading, and chondroblasts lacking beta1 integrin attached but did not spread. These data suggest that mesenchymal cells use syndecans as the initial receptor for the **ADAM** 12 cysteine-rich domain-mediated cell adhesion, and then the beta1 integrin to induce cell spreading. Interestingly, carcinoma cells attached but did not spread on **ADAM** 12. However, spreading could be efficiently induced by the addition of either 1 mM Mn(2+) or the beta1 integrin-activating monoclonal antibody 12G10, suggesting that in these carcinoma cells, the **ADAM** 12-syndecan complex fails to modulate the function of beta1 integrin.

L8 ANSWER 13 OF 20 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2000427936 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10936055
TITLE: ADAMTS9, a novel member of the **ADAM**-TS/ metallospondin gene family.
AUTHOR: Clark M E; Kelner G S; Turbeville L A; Boyer A; Arden K C; Maki R A
CORPORATE SOURCE: Department of Molecular Biology, Neurocrine Biosciences Inc., San Diego, California 92121, USA..

mclark@neurocrine.com
SOURCE: Genomics, (2000 Aug 1) 67 (3) 343-50.
Journal code: 8800135. ISSN: 0888-7543.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20000922
Last Updated on STN: 20000922
Entered Medline: 20000914

AB **ADAM**-TS/metallospondin genes encode a new family of proteins with structural homology to the **ADAM metalloprotease-disintegrin** family. However, unlike other **ADAMs**, these proteins contain thrombospondin type 1 (TSP1) repeats at the carboxy-terminal end and are secreted proteins instead of being membrane bound. Members of the **ADAM**-TS family have been implicated in the cleavage of **proteoglycans**, the control of organ shape during development, and the inhibition of angiogenesis. We have **cloned** a new member of the **ADAM**-TS/metallospondin family designated here as ADAMTS9. This protein has a **metalloprotease** domain, a **disintegrin**-like domain, one internal TSP1 motif, and three carboxy-terminal TSP1-like submotifs. In contrast to other **ADAM** -TS family members, ADAMTS9 is **expressed** in all fetal tissues examined as well as some adult tissues. Using FISH and radiation hybrid analysis, we have localized ADAMTS9 to chromosome 3p14.2-p14.3, an area known to be lost in hereditary renal tumors.

L8 ANSWER 14 OF 20 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation. on STN
ACCESSION NUMBER: 2000:927231 SCISEARCH
THE GENUINE ARTICLE: 379NL
TITLE: Cellular localization of the **disintegrin** CRII-7/rMDC15 mRNA in rat PNS and CNS and regulated **expression** in postnatal development and after nerve injury
AUTHOR: Bosse F (Reprint); Petzold G; GreinerPetter R; Pippirs U; Gillen C; Muller H W
CORPORATE SOURCE: UNIV DUSSELDORF, DEPT NEUROL, MOL NEUROBIOL LAB, MOORENSTR 5, D-40225 DUSSELDORF, GERMANY (Reprint)
COUNTRY OF AUTHOR: GERMANY
SOURCE: GLIA, (DEC 2000) Vol. 32, No. 3, pp. 313-327.
Publisher: WILEY-LISS, DIV JOHN WILEY & SONS INC, 605 THIRD AVE, NEW YORK, NY 10158-0012.
ISSN: 0894-1491.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 61
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB **Disintegrins** perform putative functions in cell adhesion, signaling and fusion. We have isolated a 2815-bp rat cDNA (CRII-7) representing a transcript that is differentially **expressed** during sciatic nerve regeneration. Nucleotide sequence comparison indicates that CRII-7 is the rat homologue to the recently **cloned** cDNAs MDC15 (**ADAM** 15) and metargidin (hMDC15) of mouse and human, respectively. The CRII-7 cDNA (rMDC15) encodes a membrane-anchored glycoprotein of approximately 85 kDa containing a **disintegrin** and a **metalloprotease** domain. Cellular **metalloprotease** **disintegrins** are a family of proteins (**ADAMs** or MDC proteins) with important roles, e.g., in cell-cell interactions during fertilization, muscle and nerve development, or tumor necrosis factor-or (TNF-cw) cleavage. Northern blot analysis demonstrated a predominant

expression of CRII-7/rMDC15 in the nervous system (PNS and CNS) and lung. Analysis of the CRII-7/rMDC15 transcript levels following peripheral nerve lesions demonstrated regulated mRNA **expression** during Wallerian degeneration and nerve regeneration. The steady-state levels of CRII-7/rMDC15 transcripts markedly increased within the first day after lesion and then steadily decreased for at least 4 weeks. CRII-7/rMDC15 mRNA **expression** was further examined during postnatal development and maturation of rat sciatic nerve and brain, as well as in cultured Schwann cells, meningeal fibroblasts, and astrocytes. In situ hybridization on paraffin sections showed the cellular localization of CRII-7/rMDC15 mRNA in Schwann cells and endothelial cells of peripheral nerve and in various neuronal populations in brain and spinal cord. (C) 2000 Wiley-Liss, Inc.

L8 ANSWER 15 OF 20 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:428698 HCAPLUS
DOCUMENT NUMBER: 134:112014
TITLE: New metalloproteinase family, ADAMTS
AUTHOR(S): Kuno, Kouji
CORPORATE SOURCE: Cancer Res. Inst., Kanazawa Univ., Japan
SOURCE: Immunology Frontier (2000), 10(3), 159-166
CODEN: IMFREG; ISSN: 0917-0774
PUBLISHER: Medikaru Rebyusha
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A review with 15 refs. on the structure and organ distribution of the ADAMTS family of metalloproteinases. **ADAM** (a **disintegrin** and metalloproteinase) family are the membranous protease participating in shedding of various mols.; ADAM17 is the tumor necrosis factor α converting enzyme (TACE). ADAMTS (**ADAM** family gene with thrombospondin motif) family are secretory proteases with thrombospondin (TSP) type 1 motif. ADAMTS-1 binds the extracellular matrix (ECM) by 3 TSP type 1 motives and spacer regions. ADAMTS-1 is **expressed** in various organs, and plays important role in formation and function of renal pelvis tissue. Anomaly in type I procollagen N-protease (pNP1, ADAMTS-2) causes disorder in dermal tissue in human Ehlers-Danlos syndrome type VIIC. Aggricase in ADAMTS family participates in degradation of cartilage **proteoglycan** in chronic rheumatoid arthritis and osteoarthritis, and it may be the therapeutic target.

L8 ANSWER 16 OF 20 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 1999263385 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10329602
TITLE: Cysteine-rich domain of human **ADAM** 12 (meltrin alpha) supports tumor cell adhesion.
AUTHOR: Iba K; Albrechtsen R; Gilpin B J; Loechel F; Wewer U M
CORPORATE SOURCE: Institute of Molecular Pathology, University of Copenhagen, Copenhagen, Denmark.
SOURCE: American journal of pathology, (1999 May) 154 (5) 1489-501.
Journal code: 0370502. ISSN: 0002-9440.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 19990614
Last Updated on STN: 20030128
Entered Medline: 19990603
AB The **ADAMs** (A **disintegrin** and **metalloprotease**) comprise a family of membrane-anchored cell surface proteins with a putative role in cell-cell and/or cell-matrix interactions. By immunostaining, **ADAM** 12 (meltrin alpha) was up-regulated in several human carcinomas and could be detected along the tumor cell membranes. Because of this intriguing staining pattern, we investigated

whether human **ADAM** 12 supports tumor cell adhesion. Using an in vitro assay using **recombinant** polypeptides **expressed** in Escherichia coli, we examined the ability of individual domains of human **ADAM** 12 and **ADAM** 15 to support tumor cell adhesion. We found that the **disintegrin**-like domain of human **ADAM** 15 supported adhesion of alphavbeta3-**expressing** A375 melanoma cells. In the case of human **ADAM** 12, however, **recombinant** polypeptides of the cysteine-rich domain but not the **disintegrin**-like domain supported cell adhesion of a panel of carcinoma cell lines. On attachment to **recombinant** polypeptides from the cysteine-rich domain of human **ADAM** 12, most tumor cell lines, such as MDA-MB-231 breast carcinoma cells, were rounded and associated with numerous actin-containing filopodia and used a cell surface heparan sulfate **proteoglycan** to attach. Finally, we demonstrated that authentic full-length human **ADAM** 12 could bind to heparin Sepharose. Together these results suggest a novel role of the cysteine-rich domain of **ADAM** 12 -- that of supporting tumor cell adhesion.

L8 ANSWER 17 OF 20 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 2003431536 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12973442
TITLE: Mechanisms of **proteoglycan** metabolism that lead to cartilage destruction in the pathogenesis of arthritis.
AUTHOR: Caterson B; Flannery C R; Hughes C E; Little C B
CORPORATE SOURCE: Connective Tissue Biology Laboratories, Cardiff School of Biosciences, Cardiff University, Wales, UK.
SOURCE: Drugs of today (Barcelona, Spain : 1998), (1999 Apr-May) 35 (4-5) 397-402.
Journal code: 101160518. ISSN: 0025-7656.
PUB. COUNTRY: Spain
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: PUBMED-NOT-MEDLINE
ENTRY MONTH: 200312
ENTRY DATE: Entered STN: 20030916
Last Updated on STN: 20031218
Entered Medline: 20031210

AB The mechanisms and agents involved in cartilage matrix destruction are poorly understood and at present there are no means of therapeutic intervention that halt or slow the degradative processes that result in tissue loss, joint space narrowing and the eventual need for surgery with total joint replacement. In recent years our laboratory has pioneered the development and use of monoclonal antibody (MAb) technologies for the study of changes in cartilage matrix metabolism in health and disease. In this chapter we have summarized results coming from our recent studies examining the mechanisms of cartilage **proteoglycan** (aggrecan) catabolism that precedes cartilage destruction in arthritis. This research has used two approaches. The first is our access to a panel of MAbs that recognize both constitutive structural epitopes and catabolic neoepitopes on cartilage **proteoglycan** metabolites. These antibodies have allowed us to determine whether the unknown proteolytic agent 'aggrecanase' or known matrix metalloproteinases (MMPs) are involved in the increased aggrecan catabolism that is observed in arthritis. Secondly, we have used reverse transcription-polymerase chain reaction (RT-PCR) techniques to profile the **expression** of members of the MMP family or **ADAMs** (A **disintegrin** and metalloproteinase) that are potentially involved in this degenerative process. Collectively, these investigations have established that aggrecanase is the major proteolytic activity responsible for aggrecan loss in the early stages that lead to cartilage degradation in arthritis. In addition, our studies have allowed us to determine many important biochemical properties of aggrecanase without knowing the identity of the enzyme. Our data also calls into question the role that MMPs may play in

the early stages of cartilage destruction that lead to surface fibrillation. However, MMPs may be involved in later stages where collagen degradation is prevalent. The role that **ADAMs** play is still unknown, although they are postulated to play an important role in shedding or activation of different classes of matrix proteases. Furthermore, we have observed changes in the patterns of cartilage **expression** in fresh tissue and model culture systems. This work has indicated clearly that there are several different classes of enzyme that can be targeted for innovative therapies which could slow or halt cartilage destruction in arthritis.

L8 ANSWER 18 OF 20 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN DUPLICATE 6

ACCESSION NUMBER: 1999263307 EMBASE
TITLE: **Expression** of ADAMTS homologues in articular cartilage.
AUTHOR: Flannery C.R.; Little C.B.; Hughes C.E.; Caterson B.
CORPORATE SOURCE: C.R. Flannery, Connective Tissue Biology Lab., Cardiff School of Biosciences, Cardiff University, Museum Avenue, Cardiff CF1 3US, United Kingdom. FlanneryCR@Cardiff.ac.uk
SOURCE: Biochemical and Biophysical Research Communications, (5 Jul 1999) 260/2 (318-322).
Refs: 22
ISSN: 0006-291X CODEN: BBRCA
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
029 Clinical Biochemistry
033 Orthopedic Surgery
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Articular chondrocytes possess the capacity to **express** a number of **ADAM** (A **Disintegrin** And Metalloproteinase) family members, thereby implicating a role for such proteins in the turnover of cartilage extracellular matrix molecules. Recently, the sequence for the human orthologue of an 'aggrecanase' isolated from bovine nasal cartilage has been elucidated, and the **recombinant** protein product shown to be capable of cleaving aggrecan specifically at the relevant peptide bonds which are hydrolyzed in situ during cartilage degradation. The sequence for the human 'aggrecanase' exhibits homology with that of murine ADAMTS-1, an **ADAM** with thrombospondin type I motifs. In the present study we have identified additional ADAMTS homologues and have examined their mRNA **expression** profiles in freshly excised human articular cartilage and in human cartilage explant cultures stimulated with IL-1, TNF-α, or retinoic acid, agents which enhance 'aggrecanase' activity in vitro. Significantly, cartilage exposed to retinoic acid showed a marked increase in the release of 'aggrecanase'-generated aggrecan catabolites with no concomitant increase in mRNA levels for any of the ADAMTS homologues investigated. These findings indicate that enhanced 'aggrecanase' activity, which may be attributed to known ADAMTS homologues, may be predominantly regulated by post-transcriptional mechanism(s), and may raise the possiblility for the existence of other as yet unidentified 'aggrecanase(s)'.

L8 ANSWER 19 OF 20 MEDLINE on STN DUPLICATE 7

ACCESSION NUMBER: 1999357011 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10429942
TITLE: Effects of culture conditions and exposure to catabolic stimulators (IL-1 and retinoic acid) on the **expression** of matrix metalloproteinases (MMPs) and **disintegrin** metalloproteinases (**ADAMs**) by articular cartilage chondrocytes.
AUTHOR: Flannery C R; Little C B; Caterson B; Hughes C E
CORPORATE SOURCE: Connective Tissue Biology Laboratories, Cardiff School of

Biosciences, Cardiff University, Wales, UK..
flannerycr@cardiff.ac.uk
SOURCE: Matrix biology : journal of the International Society for Matrix Biology, (1999 Jun) 18 (3) 225-37.
Journal code: 9432592. ISSN: 0945-053X.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF069641; GENBANK-AF069642; GENBANK-AF069643; GENBANK-AF069644; GENBANK-AF069645; GENBANK-AF069646; GENBANK-AF069647; GENBANK-AF069648; GENBANK-AF069649
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991026

AB The chondrocytes of articular cartilage synthesize a number of proteinases which are capable of degrading the component molecules of this specialized extracellular matrix. The use of class-specific proteinase inhibitors indicates that major activities responsible for catabolism of **proteoglycan** (aggrecan) and collagen are attributable to zinc-dependent metalloproteinases. In this study, we have compared the mRNA **expression** profiles of two matrix metalloproteinases (MMP-3 and MMP-13) and five **disintegrin**-metalloproteinases (**ADAM**-10, **ADAM**-9, **ADAM**-15, TNF-alpha-converting enzyme and decysin) by chondrocytes (human, porcine and bovine) from fresh cartilage and in cartilage explant cultures and isolated cells cultured in monolayer or in agarose gels. Such cultures were maintained in the presence or absence of interleukin-1 (IL-1) or all-trans-retinoic acid, two agents which promote cartilage matrix degradation in vitro. Whereas transcripts for all metalloproteinases examined were detected in chondrocytes from human osteoarthritic cartilage in monolayer cultures, mRNAs for **ADAM**-15 and decysin were not present in fresh osteoarthritic human cartilage or explant cultures. Similarly, **expression** of porcine and bovine metalloproteinase mRNAs varied with different culture conditions. Novel cDNA sequences obtained for porcine and bovine MMP-3 and MMP-13, porcine **ADAM**-10, porcine and bovine **ADAM**-9 and porcine TACE confirmed **expression** of mRNAs for these molecules by articular chondrocytes. Quantitative RT-PCR analysis was used to determine the effects of IL-1 and retinoic acid on metalloproteinase mRNA levels in human chondrocytes cultured in monolayer and in porcine chondrocytes cultured in agarose. For the MMPs, IL-1 treatment resulted in an approximately two to threefold increase in human and porcine MMP-3 and MMP-13 mRNAs, while retinoic acid treatment caused a statistically significant increase in human MMP-3 mRNA levels, but no significant change in transcript levels for porcine MMP-3 nor human or porcine MMP-13. The mRNA levels for **ADAM**-15 were elevated in human monolayer chondrocytes exposed to IL-1 or retinoic acid, while transcripts levels for TNF-alpha converting enzyme were increased in response to retinoic acid. In contrast, **ADAM**-9 mRNA levels were decreased in human monolayer chondrocytes exposed to IL-1 or retinoic acid. The results demonstrate that chondrocyte metalloproteinase **expression** can vary dependent on cell environment in situ and in vitro, and information on chondrocyte MMP and **ADAM** gene **expression** following cytokine (IL-1) or retinoid stimulation.

L8 ANSWER 20 OF 20 MEDLINE on STN
ACCESSION NUMBER: 1998157987 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9488721
TITLE: The interglobular domain of cartilage aggrecan is cleaved by hemorrhagic metalloproteinase HT-d (atrolysin C) at the matrix metalloproteinase and aggrecanase sites.
AUTHOR: Tortorella M D; Pratta M A; Fox J W; Arner E C
CORPORATE SOURCE: Inflammatory Diseases Research, The DuPont Merck

Pharmaceutical Company, Wilmington, Delaware 19880, USA.
SOURCE: Journal of biological chemistry, (1998 Mar 6) 273 (10) 5846-50.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199804
ENTRY DATE: Entered STN: 19980416
Last Updated on STN: 20000303
Entered Medline: 19980407

AB Two primary cleavage sites have been identified within the interglobular domain of the cartilage aggrecan core protein: one is between amino acid residues Asn 341 and Phe342, where many matrix metalloproteinases (MMP) have been shown to cleave; and the other is between amino acid residues Glu373 and Ala374. Although cleavage at the Glu373-Ala374 site is believed to play a critical role in cartilage aggrecan degradation in arthritic diseases, the enzyme responsible for cleavage at this site, "aggrecanase," has not been identified. Members of the **ADAM** (a **disintegrin** and metalloproteinase) family of proteins, which shows structural homology to the snake venom hemorrhagic metalloproteinases (reprolysins), have recently been demonstrated to be **expressed** in articular chondrocytes. Because many **ADAM** family members have a putative proteinase function, this raises the possibility that aggrecanase may be a member of this family of proteases. To examine whether reprolysins have the ability to cleave aggrecan at either the aggrecanase site or the MMP site, the snake venom hemorrhagic toxin metalloproteinase HT-d (atrolysin C) was tested for its ability to cleave bovine aggrecan monomer. Cleavage was monitored using the BC-3 antibody, which recognizes aggrecan fragments with the new NH2 terminus ARGSV generated by cleavage at the aggrecanase site, and with the AF-28 antibody, which recognizes aggrecan fragments with the new NH2 terminus FFGVG generated by cleavage at the MMP site. Cleavage at both the aggrecanase and MMP sites occurred in a concentration-dependent manner with 100 nM atrolysin C or greater. AF-28-reactive fragments were generated by 30 min of incubation, and levels were maximal by 8 h; BC-3-reactive fragments were detected at 2 h and continued to increase through 48 h, thus suggesting that atrolysin C can cleave at the MMP and aggrecanase sites. NH2-terminal aggrecan fragments generated by cleavage at the aggrecanase site were also detected using antisera recognizing the new COOH terminus, NITEGE, formed by cleavage at the Glu373-Ala374 bond, indicating that cleavage at this site does not require prior cleavage at the MMP site. These data provide the first demonstration that a reprolysin can cleave the core protein of aggrecan and the first example of a specific protease that can cleave at the aggrecanase site independent of cleavage at the MMP cleavage site.

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E5            2     YOSHIMURA K I/AU
E6            1     YOSHIMURA K O H/AU
E7            1     YOSHIMURA KAICHI/AU
E8            9     YOSHIMURA KAN/AU
E9            1     YOSHIMURA KANICHI/AU
E10          26     YOSHIMURA KANJI/AU
E11           1     YOSHIMURA KAORI/AU
E12           7     YOSHIMURA KAORU/AU

=> s e3
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L9         3773 "YOSHIMURA K"/AU

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E2           13     NISHIMURA/AU
E3         1725 --> NISHIMURA A/AU
E4            3     NISHIMURA A A/AU
E5            1     NISHIMURA A H/AU
E6           32     NISHIMURA A L/AU
E7          101     NISHIMURA A M/AU
E8            1     NISHIMURA ABE A/AU
E9            1     NISHIMURA AGNES/AU
E10           7     NISHIMURA AGNES L/AU
E11           2     NISHIMURA AKANE M/AU
E12           7     NISHIMURA AKEMI/AU

=> s e3
L10        1725 "NISHIMURA A"/AU

=> e hikichi y/au
E1            1     HIKICHI TOSHITAKA/AU
E2            1     HIKICHI TOSHIYA/AU
E3          286 --> HIKICHI Y/AU
E4           63     HIKICHI YASUFUMI/AU
E5          119     HIKICHI YASUO/AU
E6            1     HIKICHI YASUSHI/AU
E7           29     HIKICHI YOSHINAO/AU
E8            2     HIKICHI YOSHIYUKI/AU
E9           20     HIKICHI YUICHI/AU
E10           2     HIKICHI YUKA/AU
E11          18     HIKICHI YUKIKO/AU
E12           1     HIKICHI YUKIYOSHI/AU

=> s e3
L11         286 "HIKICHI Y"/AU

=> s l9 or l10 or l11
L12        5774 L9 OR L10 OR L11

=> d his

     (FILE 'HOME' ENTERED AT 08:49:16 ON 11 JAN 2005)

     FILE 'STNGUIDE' ENTERED AT 08:49:22 ON 11 JAN 2005

     FILE 'HOME' ENTERED AT 08:49:28 ON 11 JAN 2005

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 08:49:56 ON 11 JAN 2005
L1         18655 S "ADAM"
L2         23400 S DISINTEGRIN OR METALLOPROTEASE?
L3          2132 S L1 AND L2
L4       6866200 S CLON? OR EXPRESS? OR RECOMBINANT
L5          1478 S L3 AND L4
L6         94583 S PROTEOGLYCAN
L7            42 S L5 AND L6
L8            20 DUP REM L7 (22 DUPLICATES REMOVED)
                 E YOSHIMURA K/AU
L9          3773 S E3
                 E NISHIMURA A/AU
L10         1725 S E3
                 E HIKICHI Y/AU
L11          286 S E3
L12         5774 S L9 OR L10 OR L11
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=> s l5 and l12
L13             0 L5 AND L12

=> s l1 and l12
L14             0 L1 AND L12

=> d his

     (FILE 'HOME' ENTERED AT 08:49:16 ON 11 JAN 2005)

     FILE 'STNGUIDE' ENTERED AT 08:49:22 ON 11 JAN 2005

     FILE 'HOME' ENTERED AT 08:49:28 ON 11 JAN 2005

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L1          18655 S "ADAM"
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L4        6866200 S CLON? OR EXPRESS? OR RECOMBINANT
L5           1478 S L3 AND L4
L6          94583 S PROTEOGLYCAN
L7             42 S L5 AND L6
L8             20 DUP REM L7 (22 DUPLICATES REMOVED)
                  E YOSHIMURA K/AU
L9           3773 S E3
                  E NISHIMURA A/AU
L10          1725 S E3
                  E HIKICHI Y/AU
L11           286 S E3
L12          5774 S L9 OR L10 OR L11
L13             0 S L5 AND L12
L14             0 S L1 AND L12
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	Issue Date	Pages	Document ID	Title
1	20041223	82	US 20040259896 A1	Aza spiro alkane derivatives as inhibitors of metalloproteases
2	20040513	115	US 20040091962 A1	Proteases
3	20040429	67	US 20040081971 A1	Protein modification and maintenance molecules
4	20040429	95	US 20040081961 A1	Proteases
5	20040422	108	US 20040077048 A1	Protein modification and maintenance molecules
6	20040318	105	US 20040053269 A1	Proteases
7	20040212	106	US 20040029249 A1	Proteases
8	20040205	118	US 20040023243 A1	Proteases
9	20031218	121	US 20030232349 A1	Proteases
10	20030904	40	US 20030166899 A1	ADAMTS polypeptides, nucleic acids encoding them, and uses thereof
11	20030814	278	US 20030154032 A1	Methods and compositions for diagnosing and treating rheumatoid arthritis
12	20030703	81	US 20030124706 A1	Proteases
13	20030703	64	US 20030124579 A1	Methods of diagnosis of ovarian cancer, compositions and methods of screening for modulators of ovarian cancer

	Issue Date	Pages	Document ID	Title
14	20020808	48	US 20020107361 A1	Novel metalloproteases having thrombospondin domains and nucleic acid compositions encoding the same
15	20020711	43	US 20020090373 A1	ADAMTS polypeptides, nucleic acids encoding them, and uses thereof
16	20011206	31	US 20010049106 A1	ADAMTS polypeptides, nucleic acids encoding them, and uses thereof
17	20040120	51	US 6680189 B1	Protein and DNA thereof

	Issue Date	Pages	Document ID	Title
1	20041216	84	US 20040253602 A1	Therapeutic and diagnostic methods and compositions based on jagged/notch proteins and nucleic acids
2	20041125	104	US 20040235071 A1	Methods and compositions for treating cancer using 15986, 2188, 20743, 9148, 9151, 9791, 44252, 14184, 42461, 8204, 7970, 25552, 21657, 26492, 2411, 15088, 1905, 28899, 63380, 33935, 10480, 12686, 25501, 17694, 15701, 53062, 49908, 21612, 38949, 6216, 46863, 9235, 2201, 6985, 9883, 12238, 18057, 21617, 39228, 49928, 54476, 62113, 64316, 12264, 32362, 58198, 2887, 3205, 8557, 9600, 9693, 44867, 53058, 55556, 57658, 2208, 10252, 10302, 14218, 33877, 10317, 10485, 25964, 14815, 1363, 1397, 14827, 21708, 3801, 64698, 2179 or 13249
3	20041111	65	US 20040224378 A1	Methods for using ADAMTS-12, an integrin and metalloprotease with thrombspondin motifs
4	20041021	45	US 20040209799 A1	JAK/STAT pathway inhibitors and the uses thereof
5	20040916	35	US 20040180417 A1	Secretase/sheddase with asp-ase activity on the beta-site app-cleaving enzyme (bace, asp2, memepsin2)
6	20040708	56	US 20040132157 A1	Novel protein and DNA thereof

	Issue Date	Pages	Document ID	Title
7	20040624	217	US 20040121349 A1	Novel 27877, 18080, 14081, 32140, 50352, 16658, 14223, 16002, 50566, 65552 and 65577 molecules and uses therefor
8	20040304	32	US 20040043387 A1	Nucleic acid molecules and polypeptides related to h-ADAM7
9	20040304	207	US 20040043021 A1	Nucleotide and amino acid sequences relating to respiratory diseases and obesity
10	20040205	485	US 20040023215 A1	Novel human gene relating to respiratory diseases, obesity, and inflammatory bowel disease
11	20040108	245	US 20040006016 A1	Novel 27875, 22025 ,27420, 17906, 16319, 55092 and 10218 molecules and uses therefor
12	20040101	441	US 20040002470 A1	Novel human gene relating to respiratory diseases, obesity, and inflammatory bowel disease
13	20031113	196	US 20030212256 A1	Proteins and nucleic acids encoding same

	Issue Date	Pages	Document ID	Title
14	20030821	80	US 20030157082 A1	Methods and compositions for treating cancer using 140, 1470, 1686, 2089, 2427, 3702, 5891, 6428, 7181, 7660, 25641, 69583, 49863, 8897, 1682, 17667, 9235, 3703, 14171, 10359, 1660, 1450, 18894, 2088, 32427, 2160, 9252, 9389, 1642, 85269, 10297, 1584, 9525, 14124, 4469, 8990, 2100, 9288, 64698, 10480,20893, 33230,1586, 9943, 16334, 68862, 9011, 14031, 6178, 21225, 1420, 32236, 2099, 2150, 26583, 2784, 8941, 9811, 27444, 50566 or 66428 molecules
15	20030814	127	US 20030153018 A1	Methods and compositions for treating cancer using 2192, 2193, 6568, 8895, 9138, 9217, 9609, 9857, 9882, 10025, 20657, 21163, 25848, 25968, 32603, 32670, 33794, 54476 and 94710
16	20030807	38	US 20030148410 A1	Novel genes, compositions, kits, and methods for identification, assessment, prevention, and therapy of colon cancer
17	20030724	417	US 20030138925 A1	Novel human gene relating to respiratory diseases, obesity, and inflammatory bowel disease
18	20030417	111	US 20030073622 A1	Novel proteins and nucleic acids encoding same

	Issue Date	Pages	Document ID	Title
19	20030123	71	US 20030017572 A1	56294 and 56629, novel human metalloproteases and uses thereof
20	20021219	100	US 20020192748 A1	Novel polynucleotides and polypeptides encoded thereby
21	20020829	71	US 20020119555 A1	53014, a human metalloprotease family member and uses therefor
22	20020620	55	US 20020076778 A1	33428, a novel human metalloprotease family member and uses thereof
23	20020613	67	US 20020072490 A1	33428, a novel human metalloprotease family member and uses thereof
24	20040406	79	US 6716974 B1	Therapeutic and diagnostic methods and compositions based on jagged/notch proteins and nucleic acids
25	20040120	51	US 6680189 B1	Protein and DNA thereof

	L #	Hits	Search Text
1	L1	15150	"ADAM"
2	L2	3873	disintegrin or metalloprotease$2
3	L3	417	l1 same l2
4	L4	694595	clon$3 or express$3 or recombinant
5	L5	187	l3 same l4
6	L6	5637	proteoglycan
7	L7	17	l5 same l6
8	L8	26365	YOSHIMURA NISHIMURA HIKICHI
9	L9	25	l3 and l8